

Highlighting the Changing Landscape for Diabetes Management: New Insulins, New Pumps, and More

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Objectives

- 1) Compare and contrast insulin degludec with older insulin formulations
- 2) Given a patient case, decide if a patient is an appropriate candidate for a continuous glucose monitor (CGM) or insulin pump
- 3) Apply the use of available CGMs to a patient case
- 4) Define closed-loop insulin pump technology
- 5) Describe key features of the four most common insulin pumps available in today's market

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Disclosure

- I have no relevant financial disclosures or conflicts of interest.
- The presentation may discuss the off-label use of medications.

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Case 1

PL is a 17 yo male with T1DM who has been well-controlled on his current insulin regimen. He's starting a summer job and is concerned because the hours are variable and will include many early mornings and he is worried about missed administrations. His current insulin regimen is as follows:

- Insulin glargine 12 units QAM
- Insulin aspart
 - Breakfast – 1:10
 - Lunch – 1:7
 - Dinner – 1:7
 - Correction Factor: 1:25 over 100
- What could be done to help alleviate PL's concern?

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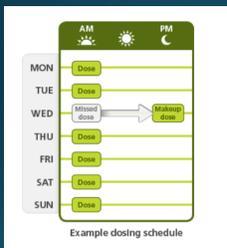
Insulin Degludec

- Ultra-long acting insulin
- Approved in children with T1DM 1 year and older
- Available as both 100 and 200 unit pens
- Long-acting mechanism
 - Insulin dihexamers make multihexamer chains in subcutaneous tissue
 - Slow dissociation leading to slow release
- Duration of action = 40 hours

J Pediatr Pharmacol Ther. 2018; 23(5):351-61.

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Marketed Advantages



FlexTouch Pen

<https://www.tresiba.com/about-tresiba/why-tresiba.html>

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Clinical Evidence – Insulin Degludec

- Urakami et al (2017)
 - Randomized crossover study of 18 children (7-14 years old)
 - Decreases in nocturnal hypoglycemia with insulin degludec
 - Non-inferior with regards to change in finger stick blood glucose values and HbA1c
- Thalange et al (2015)
 - International randomized controlled trial of 350 patients (1-17 years old)
 - Non-inferiority of HbA1c at 26 and 52 weeks
 - Reduced nocturnal hypoglycemia and hyperglycemia with ketosis
 - Increased confirmed or severe hypoglycemia

*Endocr J. 2017;64(2):133-40.
Pediatr Diabetes. 2015;16(3):164-76.*

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Other Insulin Products

- Basaglar (Insulin glargine 100 units/mL)
 - Insulin glargine product manufactured by Eli Lilly and Company
 - Approved for patients > 5 years of age
 - Lower average wholesale price
- Toujeo (Insulin glargine 300 units/mL)
 - Not approved in pediatrics
 - Slower onset of action compared to Lantus
 - Phase 3 study completed (EDITION JUNIOR)



J Pediatr Pharmacol Ther. 2018; 23(5):351-61.

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Long-acting Insulin Comparison

Brand (Generic)	Age Approval	Concentration (s)	Units per Pen	Stability once opened	Comments
Tresiba (insulin degludec)	≥ 1 yr	100 units/mL; 200 units/mL	U-100 – 300 units U-200 – 600 units	56 days	Half-life – 25 hours, Duration – 42 hours
Basaglar (insulin glargine)	≥ 6 yr	100 units/mL	300 units	28 days	
Lantus (insulin glargine)	≥ 6 yr	100 units/mL	300 units	28 days	
Toujeo (insulin glargine)	≥ 19 yr	300 units/mL	450 units	56 days	
Levemir (insulin detemir)	≥ 2 yr	100 units/mL	300 units	42 days	

J Pediatr Pharmacol Ther. 2018; 23(5):351-61.

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On the Horizon – Insulin Technologies

- Pens with memory functions
 - HumaPen Memoir (Lilly)
 - NovoPen Echo (Novo Nordisk)
- Caps with ability to track past doses
- Pens with Bluetooth connectivity

Nature Reviews Endocrinology. 2018; 14: 464-75.

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Case 1

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- Insulin aspart
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Case 1 Question

- Which of the following would you choose for PL?
 - Switch to insulin degludec 12 units QAM
 - Switch timing of insulin glargine to 12 units QHS
 - Continue insulin glargine 12 units QAM
 - Switch to insulin detemir 12 units QHS

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Case 1 Follow-Up

- PL returns in one week with the following blood glucose log. He remains on 12 units of the long-acting insulin that you recommended at his previous visit and has been adherent to therapy with his new job.

Morning/Breakfast	Lunch	Dinner	Bedtime
95	150	91	56
104	170	94	95
110	180	150	72
160	99	104	102
86	102	115	81
92	195	95	70
100	140	88	66

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Insulin Management

- Which of the following changes would be best for PL's insulin?
 - Insulin aspart
 - Breakfast – 1:10
 - Lunch – 1:7
 - Dinner – 1:7
 - Correction Factor: 1:25 over 100

- Change lunch to 1:10
- Change breakfast to 1:8 and dinner to 1:8
- Change breakfast to 1:12 and dinner to 1:6
- Change lunch to 1:8 and dinner to 1:8

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Case 2

- HF is an 8 yo male with T1DM (diagnosed at age 5) who is currently on an insulin pump. He has been doing self-monitoring of blood glucose and his diabetes has been well-controlled (A1c = 6.9%). He participates in several sports and is very active. His parents are very concerned about hypoglycemia.

Is HF a candidate for a continuous glucose monitor?

- Yes
- No

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What is a Continuous Glucose Monitor?

- Device permitting near constant analysis of blood glucose
 - Generally recorded every 1-5 minutes
 - Measures interstitial fluid glucose
- Provides immediate information to the user
- Tracks glucose trends
 - Direction of change
 - Rate of change

*Diabetes Care. 2018; 41:2265-74.
Adv Ther. 2019; Epub ahead of print. doi: 10.1007/s12325-019-0870-x.*

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Types of CGMs

- Real-time CGM (rtCGM)
 - Automatic transmission of data to the user
 - Provides alerts and/or alarms
 - Transmits data to a receiver
 - Common type encountered in pediatrics and Type 1 diabetes mellitus
- Intermittently Scanned CGM (isCGM)
 - Requires user to scan the sensor to get alerts
 - No alerts or alarms

*Diabetes Care. 2018; 41:2265-74.
Adv Ther. 2019; Epub ahead of print. doi: 10.1007/s12325-019-0870-x.*

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Why not Hemoglobin A_{1c}?

- Benefits
 - Rigorously standardized
 - Drawn in non-fasting state
 - Widely available
 - Useful for population health
 - Intermediate outcome measure for complication risk as well as treatment efficacy

HOWEVER.....

*Diabetes Care. 2018; 41:2265-74.
Adv Ther. 2019; Epub ahead of print. doi: 10.1007/s12325-019-0870-x.*

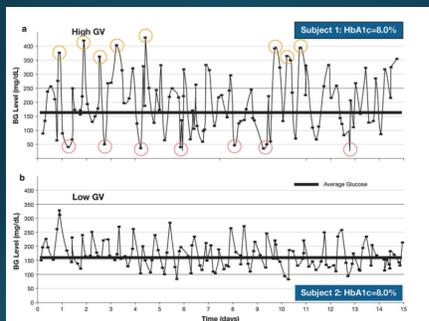
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Limitations to A1C

- Does NOT reflect daily fluctuations, variability, or time in range
- Does NOT show intra or inter-day excursions with subsequent hypoglycemia or hyperglycemia
- Unreliable with certain conditions
 - Anemia
 - Hemoglobinopathies
 - Cystic Fibrosis
 - Pregnancy
- Applies a population average to the individual

Diabetes Care. 2018; 41:2265-74. Adv. Ther. 2019; Epub ahead of print. doi: 10.1007/s12325-019-0870-x.

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Diabetes Care. 2016; 39:502-10.

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Why not Self-Monitored Blood Glucose (SMBG)?

- Benefits
 - Cost-effective means of obtaining data
 - Easily accessible
 - Easy to train patients

HOWEVER.....

Diabetes Care. 2018; 41:2265-74. Adv. Ther. 2019; Epub ahead of print. doi: 10.1007/s12325-019-0870-x.

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Limitations to SMBG

- Finger Sticks may not be acceptable to patients
- May not be feasible/desirable
- Susceptible to user error
- Many systems do not meet recommended standards
- "Point in Time" Measure
- May miss periods of hypoglycemia
- Strips may be of variable quality
- Inconvenient and painful

Diabetes Care. 2018; 41:2265-74.
Adv Ther. 2019; Epub ahead of print. doi: 10.1007/s12325-019-0870-x.

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Benefits to CGM

- Comprehensive picture
- No "Missed" readings
- Many different metrics can be assessed
- Fairly simple to use
- May be pre-calibrated

Diabetes Care. 2018; 41:2265-74.
Adv Ther. 2019; Epub ahead of print. doi: 10.1007/s12325-019-0870-x.

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Limitations to CGM

- More expensive
- Relatively complex training requirements
- High level of compliance and patient interaction required
- May need multiple fingersticks
- Sensor is constantly worn

Diabetes Care. 2018; 41:2265-74.
Adv Ther. 2019; Epub ahead of print. doi: 10.1007/s12325-019-0870-x.

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Selecting a Monitoring Plan

TJ is a 16 yo female with obesity, asthma, and type 2 diabetes. She is currently on Lantus 18 units SC nightly as well as metformin XR 1 g po BID. Her adherence to metformin is near perfect, but is suboptimal to Lantus because she does not like doing an injection.

Which of the following would you use to routinely monitor TJ's diabetes management?

- A. A₁C
- B. SMBG
- C. CGM

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Discussion

- What types of patients would most benefit from the use of a CGM?

- Would you use a CGM in a type 2 patient?

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Currently Approved CGMs

Real-Time Sensors

- Medtronic Enlite
- Medtronic Guardian 3
- DexcomG5
- DexcomG6
- Eversense

Intermittently-Scanned

- FreeStyle Libre

Diabetes Care. 2018; 41:2265-74.

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Components to Medtronic/Dexcom CGMs

- 1) Disposable sensor
 - Inserted into subcutaneous tissue to measure glucose
- 2) Transmitter
- 3) Receiver
 - Stand-alone device
 - Pump
 - Smartphone/Smartwatch

Diabetes Care. 2018; 41:2265-74.

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Medtronic Enlite

- Component of the MiniMed 530G, 630G, and 640G insulin pumps
- May alter basal rates without confirmatory testing
- Less optimal performance on day 1
- Being phased out



Diabetes Care. 2018; 41:2265-74.

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Medtronic Guardian 3

- Component of MiniMed 670G insulin pump
- Approved as a stand-alone sensor (Guardian Connect)
- Predictive High/Low alerts 10-60 minutes ahead of time
- May alter basal rates without confirmatory testing
- Less tubing than previous Medtronic sensors



Diabetes Care. 2018; 41:2265-74.
<https://www.medtronicdiabetes.com/products/guardian-sensor-3>. Accessed 19 Feb 2019.

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Dexcom G5

- Stand-alone device for use with both pumps or injection therapies
- Interfaces with many devices/apps
- Use with a data sharing app is approved by Medicare
- Remote monitoring possible



Diabetes Care. 2018; 41:2265-74.
<https://www.dexcom.com/g5-mobile-cgm>. Accessed 15 Feb 2019.

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Dexcom G6

- Stand-alone device for use with both pumps or injection therapies
- Interfaces with many devices/apps
- First FDA approval in Class II special controls
- Optional "Urgent Low Soon" feature
- Factory calibrated, but can also be manually calibrated
- No interference with acetaminophen
- Share data with up to 5 sensors



Diabetes Care. 2018; 41:2265-74.
<https://www.dexcom.com/g6-cgm>. Accessed 15 Feb 2019.

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Eversense rtCGM

- Implantable, fluorescence-based glucose sensor
- Removeable external smart transmitter
- Mobile medical application
- Approved for 180 day wear time in Europe, 90 days in US
- Twice daily calibration required
- Only approved for adjunctive use



Diabetes Care. 2018; 41:2265-74.
<https://www.eversenseddiabetes.com/products/>. Accessed 15 Feb 2019.

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FreeStyle Libre Flash

- Two components
 - Combined glucose sensor/transmitter (in upper arm)
 - Touch-screen reader device
- 12-hour warm-up time
- No initial/daily calibration required
- 8 hours of data at a time
- Approved for non-adjunctive use
- Approved in patients > 18 years old



Diabetes Care. 2018; 41:2265-74. <https://www.freestyle.us>. Accessed 15 Feb 2019.

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Summary Table

Feature	FreeStyle Libre	Dexcom G6	Dexcom G5	Guardian 3	Enlite	Eversense
Age Approved	≥ 18 (US), ≥ 4 (Int'l)	≥ 2	≥ 2	≥ 7	≥ 16	≥ 18
Wear time (Days)	14	10	7	7	6	≤ 90 (US), ≤ 180 (Int'l)
Calibration Required	No	No	2 x daily	2 x daily	2 x daily	2 x daily
Warm-up Period	1	2	2	2	2	24
Real-time Remote Sharing	No	Yes	Yes	No	Yes	No
Interoperability	No	Yes	Yes	No	Yes	Yes
Overall Accuracy (Mean absolute relative Difference)	9.7	9	9	10.6	16.1	8.8

Diabetes Care. 2018; 41:2265-74.

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Notes on Accuracy

- Critically important for patient adherence
 - Alarm fatigue if appropriately set alarms are not working
 - User trust in reliability/accuracy tied to continued use
- Difficult to directly compare various systems based on differences in study design and methodology

Diabetes Care. 2018; 41:2265-74.

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Clinical Evidence for CGMs

- Most large trials are in adult patients
 - DIAMOND
 - T1DM and T2DM patients with multiple daily injections
 - Improvements in A1c, time in hypoglycemia and hyperglycemia
 - Less diabetes-related distress
 - IN CONTROL
 - T1DM patients with hypoglycemia unawareness
 - Significantly more time in normoglycemia and less severe hypoglycemia
 - HypoE (Hypoglycemia in Deutschland)
 - T1DM patients with multiple daily injections and problematic hypoglycemia
 - Reduced low glucose events and episodes of severe hypoglycemia

Diabetes Care. 2018; 41:2265-74.

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Case 2

- HF is an 8 yo male with T1DM (diagnosed at age 5) who is currently on an insulin pump. He has been doing self-monitoring of blood glucose and his diabetes has been well-controlled (A1c = 6.9%). He participates in several sports and is very active. His parents are very concerned about hypoglycemia.

Is HF a candidate for a continuous glucose monitor?

- A. Yes
- B. No

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Case 2 Discussion

- What benefits might HF see from the use of a CGM?
- What potential disadvantages would a CGM pose?
- What counseling points would you have for HF's parents prior to starting?

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Case 2 Follow-up

• Which of the following CGMs would you choose for HF?

- A. FreeStyle Libre
- B. Dexcom G6
- C. Eversense
- D. Medtronic Enlite

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Highlights: CGMs

- CGMs will continue to become more present in the DM community for both patients on pump therapy and those on multiple daily injections
- Advances in technology have improved key characteristics such as integration with pumps, alert/alarm features, and wear time
- Patients should be assessed for readiness prior to starting a CGM

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Audience Question

Which of the following patients would be the best candidate for the use of an insulin pump?

- A. A 15 yo female newly diagnosed with T₁DM
- B. A 5 yo male with T₁DM and an A₁C of 9% and frequent episodes of hypoglycemia
- C. A 10 yo male with T₁DM an A₁C of 6.8% and relatively few hypo or hyperglycemia episodes
- D. A 17 yo female with T₂DM and an A₁C of 9% currently on oral therapies only

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Insulin Pumps

- First available in the 1970s
 - Incredible increase in use in recent years
 - > 1 million worldwide users
 - 40-60% of the T1DM population in Western countries
- Deliver rapid-acting insulin into subcutaneous tissue at preprogrammed rates
 - Rates are either hourly or every half hour
 - User-directed boluses
- Site changes – every 3 days

Nature Reviews Endocrinology. 2018; 14: 464-75.

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Benefits of Insulin Pumps

- Convenience
 - Fewer injections
 - Easier to adjust to life changes
 - No need to keep track of various insulin pens/vials
- Increased consistency in insulin response
- Tracking features

Pumping Insulin, 5th ed. San Diego, Torrey Pines Press. 2012.

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Limitations

- Being "Attached"
- Weight Gain
- Site Infections
- Ketoacidosis
- Cost

Pumping Insulin, 5th ed. San Diego, Torrey Pines Press. 2012.

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Tethered Pumps v. Patch Pumps

- Tethered Pump
 - Insulin reservoir connected to transcutaneous cannula via tubing of ~ 18-42 inches
 - Tucked into pockets or worn on the user
- Patch Pump
 - Short insulin infusion set which is a part of the pump itself
 - Attached directly to user's skin
 - Do not require disconnecting for activity

Nature Reviews Endocrinology. 2018; 14: 464-75.

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Evidence for Pump Use in Pediatrics

- Less conclusive than data in adults
- Similar to lower A₁C compared to multiple daily injections
 - Inconclusive benefit in younger children
- Higher treatment satisfaction
- Similar risk of diabetic ketoacidosis
- Lower daily insulin requirement

Nature Reviews Endocrinology. 2018; 14: 464-75.

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American Academy of Clinical Endocrinology (AACE) Recommendations

- A₁C above goal on injection therapy
- Frequent and/or severe hypoglycemia
- Pronounced dawn phenomenon
- Prone to ketosis
- Fluctuating glucose
- Needle phobia
- Microvascular complications
- Very young children
- Athletes
- Adolescents with eating disorders
- Pregnant teenagers

Endocr Pract. 2015; 22: 231-61.

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General Pump Features

- Bolus calculators
- Bolus profiles
- Temporary Basal rates
- Alarms/Alerts
 - Suspend on Low
 - Suspend before Low

Nature Reviews Endocrinology. 2018; 14: 464-75.

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Expectations on Insulin Pumps

1. I'll have perfect control.
2. By counting carbs, I can eat when I want.
3. I'll check my glucose more often and get better control.
4. Complications won't happen.
5. It will be easy.
6. Knowing my blood glucoses, basal and bolus dose, I can adjust settings to improve my control

Pumping Insulin, 5th ed. San Diego, Torrey Pines Press. 2012.

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Tandem t:slimX2 and t:flex

Positive Highlights

- iPod/iPhone like appearance
- Fairly compact/thin
- Fastest bolus entry amongst pumps
- T:flex holds up to 480 units
- Charges (no batteries)
- X2 coordinates with G6 and Basal IQ technology
- Site-change reminder feature
- Alerts for high temperature
- Limits unintended insulin movement



<https://www.tandemdiabetes.com/products>. Accessed 8 Feb 2019.

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Tandem pumps – Potential Limitations

- Lacks the "Auto" Mode available with latest Medtronic model
- Small buttons
- Requires purchase of case with clip
- Tubing connector can snag
- Tubing is proprietary
- No linking meter
- Charging required 1-2 x per week

<https://www.tandemdiabetes.com/products>, Accessed 8 Feb 2019.

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Medtronic MiniMed 630G



- Previously coordinated with Enlite CGM
- Automatic basal shutoff with low glucose detected
- "Connect" feature available to share data
- Full-color screen
- Can store frequently used basal/temporary settings
- Integrated meter
- Choice of slow or fast boluses
- Waterproof up to 12 feet for 24 hours

<https://www.medtronicdiabetes.com/products/minimed-630g-insulin-pump-system>, Accessed 8 Feb 2019.

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Limitations – MiniMed 630G

- Can be somewhat difficult to use/program
 - Extra buttons to push/confirmation steps
 - Multiple menus/programming features
- Smaller screen/text
- Restricted downloading of information
- Insulin-on-board only deducted from corrections

<https://www.medtronicdiabetes.com/products/minimed-630g-insulin-pump-system>, Accessed 8 Feb 2019.

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Closed Loop Technology

- "Auto" Mode
 - Basal adjustment occurs without user programming
 - Data from CGM assessed every 5 minutes
 - Uses point-in-time glucose along with trends/patterns and predictive algorithms to adjust delivery rate
 - Includes suspend on low and before low options
- User programming is still required for meal-time boluses

<https://www.medtronicdiabetes.com/products/minimed-670g-insulin-pump-system>, Accessed 8 Feb 2019.

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Medtronic MiniMed 670G



First "closed-loop" system



Displays CGM data directly on screen

<https://www.medtronicdiabetes.com/products/minimed-670g-insulin-pump-system>, Accessed 8 Feb 2019.

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Additional Highlights – Medtronic 670G

- Ability to store frequently used boluses and temporary basal settings
- Full-color screen
- Attachable clip
- Integrated meter
- Choice of slow or fast boluses
- Waterproof up to 12 feet for 24 hours

<https://www.medtronicdiabetes.com/products/minimed-670g-insulin-pump-system>, Accessed 8 Feb 2019.

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Medtronic MiniMed 670G – Potential Limitations

- Additional fingersticks required for "airplane mode" CGM option
- Automode requires user skill to use effectively
- Relatively small screen/text
- Restricted downloading of information
- Insulin-on-board only deducted from correction boluses

<https://www.medtronicdiabetes.com/products/minimed-670g-insulin-pump-system>, Accessed 8 Feb 2019.

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Insulet OmniPod



- Patch Pump + Personal Diabetes Manager (PDM)
- Discrete pump size
- No tubing
- No disconnecting/reconnecting
- Automated cannula insertion
- Possible less risk for absorption problems ("Forced site changes")
- Watertight
- New DASH system with VIEW app

<https://www.myomnipod.com/home>, Accessed 8 Feb 2019.

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Potential Limitations - OmniPod

- Not yet fully integrated with CGM technology
- Programmer somewhat bulky
- May be conspicuous
- Can not make changes or give boluses without PDM
- Cannot edit anything while bolus is given
- Max reservoir – 200 units
- Stops working after 72 hours
- Dislodged or clogged cannula requires complete replacement
- No vibrate option

<https://www.myomnipod.com/home>, Accessed 8 Feb 2019.

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Patient Considerations for Choosing a Pump

1. Personal Appeal
2. Easiness of Programming
3. Ease of Use
4. Reminders/Alarms
5. Fine-tuning of programming
6. Basal on Board features
7. Activity Level
8. Choice of infusion sets
9. Customer Service
10. Insurance coverage

Pumping Insulin, 5th ed. San Diego, Torrey Pines Press. 2012.

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Discussion

- Which patients might most benefit from the use of the MiniMed670G insulin pump?

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Selecting a Pump

- JG is a 15 yo male with T1DM (A1C = 8.2%) who is extremely active. He plays soccer and swims for his high school team. He is interested in starting pump therapy for better management of his blood sugars. Which of the following would be the best choice for JG?

- A. Tandem t:slim
- B. Medtronic MiniMed 630G
- C. Medtronic MiniMed 670G
- D. Insulet OmniPod

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Summary

- Novel technologies are available to improve the management of pediatric patients with diabetes
- New insulins provide more flexible dosing schedules for children with busy schedules
- Continuous glucose monitors are an attractive option for monitoring glucose trends and clinical decision-making
- Insulin pumps continue to get "smarter" and will allow for tighter control moving forward

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